## TPP1 OB-Fold Domain Controls Telomere Maintenance by Recruiting Telomerase to Chromosome Ends.

**Journal:** Cell

**Publication Year:** 2012

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**PubMed link:** 22863003

**Funding Grants:** Stanford CIRM Training Program

**Public Summary:**
Telomerase is a multi-subunit reverse-transcriptase enzymatic complex that serves a crucial function in human cancer by synthesizing telomeres and supporting cancer cell immortalization. A fundamental step in the regulation of telomerase is its recruitment to telomeres, which depends on its interaction with telomere-binding proteins. In this work, we show that a specific region of the telomere-binding protein TPP1 (the OB-fold domain) recruits telomerase to telomeres through an association with the telomerase reverse transcriptase, TERT. We show that this domain is sufficient to recruit telomerase and that the expression of the TPP1 OB-fold alone is sufficient to inhibit telomere maintenance by blocking access of telomerase to its cognate binding site at telomeres. This work has potential implications for cancer therapies, since potential inhibitors could disrupt the interaction between TPP1 and telomerase, leading to impaired telomere maintenance in cancer cells.

**Scientific Abstract:**
Telomere synthesis in cancer cells and stem cells involves trafficking of telomerase to Cajal bodies, and telomerase is thought to be recruited to telomeres through interactions with telomere-binding proteins. Here, we show that the OB-fold domain of the telomere-binding protein TPP1 recruits telomerase to telomeres through an association with the telomerase reverse transcriptase TERT. When tethered away from telomeres and other telomere-binding proteins, the TPP1 OB-fold domain is sufficient to recruit telomerase to a heterologous chromatin locus. Expression of a minimal TPP1 OB-fold inhibits telomere maintenance by blocking access of telomerase to its cognate binding site at telomeres. We identify amino acids required for the TPP1-telomerase interaction, including specific loop residues within the TPP1 OB-fold domain and individual residues within TERT, some of which are mutated in a subset of pulmonary fibrosis patients. These data define a potential interface for telomerase-TPP1 interaction required for telomere maintenance and implicate defective telomerase recruitment in telomerase-related disease.